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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 14

Serial Number: 08/393,066
Filing Date: February 23, 1995
Appellant(s): Wolfe and Fraser

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Jane Massey Licata
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed May 16, 1997.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct. However, a more concise statement of the status of the claims is as follows:

In the final action mailed September 13, 1996, claims 1-9 are rejected under 35 U.S.C. 112 as lacking enablement, claims 1,2,5 and 6 are rejected under 35 U.S.C. 102 as being anticipated by Dobson et al, and claims 3,4,7,8 and 9 are rejection under 35 U.S.C. as being obvious over Dobson et al in view of Nishimura.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-9 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Dobson et al (1989) "Identification of the Latency-Associated Transcript Promoter by Expression of Rabbit Beta-Globin mRNA in Mouse Sensory Nerve Ganglia Latently Infected with a Recombinant Herpes Simplex Virus" Journal of Virology 63, 3844-3851.

Nishimura et al (1986) "Nucleotide Sequence of Rat Preputial Gland β-Glucuronidase cDNA and *in vitro* Insertion of its Encoded Polypeptide into Microsomal Membranes", Proceedings National Academy of Sciences (USA), 83, 7292-7296.

(10) New Prior Art

No new prior art has been applied in this examiner's answer.

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

Claims 1-9 are drawn to a method of delivering a gene to the central nervous system of a mammal, comprising administering a neurotropic virus containing a DNA sequence of interest where the DNA sequence of interest is operatively linked to a promoter. This invention resides in the general arena of in vivo delivery which is part of gene therapy. The delivery of a gene is a prerequisite for any sort of in vivo expression or any sort of gene therapy.

However, the specification does not provide an enabling use for mere delivery absent a therapeutic outcome. In fact the specification is very clear that the purpose of the delivery method to produce a gene therapy (specification, page 2, line 3 to page 3, line 17; page 8, lines 9-13; page 9, line 34 to page 10, line 9; page 16, lines 1-17 and page 20, lines 7-10). At each of these citations, the specification discloses that the method can be used to delivery genes to the CNS to treat a variety of diseases such as Parkinson's Disease and Lesch-Nyhan Disease. The specification does not disclose a use for the claimed method of delivery absent a treatment. As the artisan reads the specification to gain guidance on the making and using of an invention, the artisan would see only that the claimed method has a use as a gene therapy. The art does not provide guidance to other uses for in vivo gene delivery absent a therapy. Thus, the claims are not enabled when read in view of the specification.

Status of the Art

At the time of filing, gene therapy was not developed sufficiently that the mere showing of delivery of a gene to a particular tissue would have been viewed as enabling gene therapy. To achieve a therapeutic effect, an amount of a neurotropic viral vector would need to be delivered to the appropriate tissue and expressed sufficiently to provide and alleviation of some symptoms associated with a particular disease. As the art fails to supply the necessary teachings, it is incumbent on the specification to do so. While the specification need not disclose that which is know in the art at the time of filing, the

corollary, the specification need to discloses that which is not known in the art at the time of filing, applies. While the skill level in gene therapy is considered to be high, the skilled artisan would need guidance on treatment protocols to achieve a therapeutic result from the method of delivery.

Working Examples and Guidance

The guidance provided in the specification is not seen as sufficient to enable a gene therapy method. Appellant has not shown that the claimed method can deliver and express a gene sufficiently to cause the amelioration of symptoms associated with a disease. Appellant has not provided guidance as to which promoters would regulate expression sufficiently to achieve a therapeutic effect. The achieving of such expression levels is necessary requirement for gene therapy. Examples 4 and 5 (specification, pages 25-26) teach that the administration, by corneal abrasion, of an HSV vector comprising the DNA sequence for β- glucuronidase (GUSB) operatively linked to the HSV LAT promoter to adult MPS VII mice results in the detection of β-glucuronidase in brain and trigeminal ganglia (a facial nerve) of the mice. However, the mice, where are models for mucopolysaccharidosis VII due to mutations in their GUSB gene, are not described as showing any alleviation of symptoms associated with the disorder due to the treatment. The specification states that the expression of the GUSB gene for 4 months in brain and trigeminal ganglia re presents increases the therapeutic presence of ameliorative enzymes for a lysosomal

storage disease (specification, page 26, lines 2-6). However, there is no evidence that the level of expression achieved, which was not specifically stated, correlates to a treatment for mucopolysaccharidosis VII or any other CNS associated disorder. The specification provides no guidance as to routes of delivery, promoters or neurotropic viral vectors to enable a therapy. Thus the instant specification is an invitation to the artisan to develop an effective method of treating a CNS related disorder by administering a neurotropic virus.

The rejections under 35 U.S.C. 102 and 35 U.S.C. 103 have been replaced by the rejection under 35 U.S.C. 103 in the new ground of rejection. Appellant's arguments are answered to the extent possible in the section "Response to Arguments.

(12) New Ground of Rejection

This examiner's answer contains the following NEW GROUND OF REJECTION.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1- 9 are rejected under 35 U.S.C. § 103 as being unpatentable over Dobson et al (1989) J. Virol. 63, 3844-3851 in view of Nishimura et al (1986) Proced. Natl. Acad. Sci. 83, 7292-7296 . Dobson teaches the delivery of the rabbit ß-globin gene to the peripheral nervous system (PNS) of mice where expression of the ß-globin gene is

regulated by the HSV-1 latency promoter (page 3850, col. 1, parag. 4, lines 1-6, page 3847, figure 5). The HSV-1 vector is administered by foot pad injection which is a peripheral inoculation (page 344, col. 2, parag. 1, lines 4-6). Dobson does not teach the delivery to the CNS or the delivery of β- glucuronidase operatively or tyrosine hydroxylase linked to a promoter. However, Nishimura teaches the DNA sequence for β-glucuronidase (page 7294, figure 3). Motivation is offered by Dobson in stating that HSV-1 is an vector for the transfer of genes to neurons (page 3850, col. 2, parag. 3, lines 1-2). Further motivation is found in Dobson's teachings that HSV can produce latent infections in both the PNS and the CNS, and that the latency activated promoter, the LAT promoter, is active in such infections (page 3844, col. 1, parag. 1, lines 1-7). Thus given the teachings of Dobson that an HSV-1 vector delivers a gene of interest to the PNS and regulates expression of the gene from the LAT promoter, and that HSV inherently infects both the PNS and CNS, it would have been obvious to the ordinary artisan had at the time of filing to deliver any gene of interest to the CNS by administering the vector of Dobson. Absent results to the contrary, the ordinary artisan at the time of filing would have had a reasonable expectation of success in delivering, and expressing, a gene of interest by administering an HSV-1 vector comprising a gene of interest operatively linked to the LAT promoter. Methods for the insertion of DNA sequence of interest, as described in Nishimura, into recombinant HSV-1 vectors ,as described in Dobson, would have been within the scope of skills of the ordinary artisan at the time of the instant invention. Dobson also teaches that three HSV-1 strains have been sequenced in the latency region, and that they have the same structure, of which is HSV-1 strain 17syn+ (page 3844, col. 1, parag. 2). Thus

absent results to the contrary, all strains of HSV-1 would contain the LAT promoter at the same location on the viral genome so that the teachings of Dobson could be applied to each HSV-1 strain. Thus for gene delivery to the CNS, Dobson in view of Nishimura offers sufficient teachings and motivation for the ordinary artisan to make and use the claimed invention at the time of filing.

(13) Response to argument

A. Enablement Rejection

In summary, claims 1-9 are drawn to a method of delivering a gene to the central nervous system of a mammal, comprising administering a neurotropic virus containing a DNA sequence of interest where the DNA sequence of interest is operatively linked to a promoter. The rejection is based on the premise that claims are read in light of the specification, and that when the instant claims are read in light of the instant specification, the method of delivering a gene is disclosed only with the context and confines of a therapy. The specification does not disclose, or enable, a reason for the method of delivery absent a therapeutic outcome (specification, page 2, line 3 to page 3, line 17; page 8, lines 9-13; page 9, line 34 to page 10, line 9; page 16, lines 1-17 and page 20, lines 7-10). Thus the artisan would not know how to make and use the claimed invention given the teachings in the art or the specification at the time of filing.

Appellant argues that a demonstration of therapeutic benefit is not a requirement of patentability. Appellant argues that they are not required to prove that a correlation

exists between a particular activity and a therapeutic use. Applicant argues that the court has held that all is required is a reasonable correlation between activity and the asserted use. Appellant cites *Nelson V Bowler 206 USPQ 881* and MPEP 2107.02. Appellant also argues that evidence from in vivo testing should be considered sufficient to support the credibility of the asserted utility. Appellant cites *In re Hartop* 135 USPQ 419; *In re Krimmell* 130 USPQ 215 and *Ex parte* Krepelka 231 USPQ 746. These arguments are not persuasive.

The claimed invention must be enabled. While a therapeutic benefit is not necessarily necessary for patentability, such a benefit must be provided by the specification with a reasonable expectation of success without an undue amount of experimentation. For the instant claims, when they are read in light of the specification, the only reason the artisan would find to use the method is for gene therapy procedures. Thus for the instant claims, a therapeutic use must be enabled by the specification. The term "therapy" does not have to be present for the claims to be read as a therapy if the specification discloses no other uses for delivery of a gene. The question still arises as how would the artisan know how to use the claimed invention given the specification. The answer is as a therapeutic protocol. In this within this context that the rejection has been made. Appellant has not shown where in the specification another use is asserted or enabled. Thus the claims are seen as a therapeutic method. As a therapy, there must be a correlative between the administration of the neurotropic virus and an alleviation of symptoms. The specification only shows the expression of one DNA sequence administered within one vector and by one route of delivery, and that expression level is

not shown to be sufficient to provide an alleviation of symptoms. There is no evidence that an alleviation of symptoms can be achieved by the claimed vector. This is in addition to the art not providing guidance that the artisan can rely on for achieving expression levels sufficient to achieve a therapy. Further, each of applicant's cited court or Board of Appeals decisions, or MPEP cite pertains to utility rejections under 35 U.S.C. 101. A utility rejection is not of record in this case, and appellant has not explained how these cases are related to the enablement rejection of record. Utility and Enablement are different concepts with different requirements. An invention can have utility but not be enabled. The instant claims have utility, but they lack enablement. There is nothing in the cited decisions which address the instant situation, where the rejection is the specification does not teach the artisan how to use the claimed invention.

Appellants have submitted a declaration by Dr. Laura Plunkett to support there arguments of therapeutic utility. Appellants have supplied a chapter from Goodman & Gillman's The Pharmacological Basis of Therapeutics on gene therapy to support their arguments. Appellant's argue that pharmacologists view gene therapy as another tool for drug delivery. Appellant argues that the examiner has dismissed the data and teachings in the specification because one is skeptical of gene therapy. This is not persuasive.

Declarant Plunkett has specifically addressed the issue of "utility" , but as stated above this is a non-issued in the instant prosecution, as the rejections are enablement. However, the issues raised by declarant will be addressed within the context of "enablement". Declarant states that for utility, it is necessary to demonstrate a pharmacological effect. Declarant states that the delivery and expression of a gene to the

CNS is a pharmacological effect. Declarant states that a therapy can not be successful unless the target cells are reached and effectively altered. It is agreed that delivery and expression has been shown. This was done in previous office actions. The rejection is not whether or not a DNA sequence can be delivered or expressed, but does the delivery and expression have an enabled use within the confines of the specification. As the specification discusses therapy as the use for the delivery method, and no alleviations of symptoms has been shown, the delivery method is not enabled. The artisan has been given no guidance in the specification to achieve a therapeutic outcome. The demonstration in the specification of expression of the GUSB gene does not suffice a therapy. This demonstration is a partial method which could possibly lead to a therapy if someone else determine routes of delivery, virus vectors, amounts of virus to be administered and the frequency of administration that lead to a therapy. While some sort of guidelines to provide a reasonable expectation of success in achieving a therapy, the claims are not enabled. There is no evidence of record that the target cells, in the words of declarant, are effectively altered with the confines of the specification, which is gene therapy. While other routes of delivery, such as those disclosed in the specification, made lead to mere delivery, there is no expectation of success that a gene therapy will be achieved by any other disclosed neurotropic virus or any other route of delivery. Such is not correlated in the specification and such is not taught in the art. Declarant also states that the FDA accepts for clinical trials evidence that a compound has good pharmacological activity in animals. Declarant states that therapeutic effect or benefit of a treatment strategy is the standard applied in the FDA drug approval process. To date

there is no case law, board decisions or office policy that equates the FDA process for clinical trials with patentability. Thus that which is required by the FDA does not mean that any statute pertaining to patentability has been reached. It is noted that pharmacological activity does not mean that a therapeutic benefit has been achieved. It is conceivable that a drug could have pharmacological activity and not provide an alleviation of symptoms. Such is frequently seen. If one has a headache and takes a pain reliever, yet retains the headache, this does not mean there is no pharmacological activity associated with the pain reliever, but the degree of activity is insufficient to affect the headache. DNA and genes are new types of drugs, and the effective pharmacological activities of these new drugs has not been taught at being sufficient to alleviate symptoms of a disease or condition such that the specification need not supply such teachings. Exhibit 3, Goodman and Gillman, chapter 8, page 81, col.2, parag. 2, states that the delivery of exogenous DNA and its processing by target cells requires new pharmacokinetics paradigms beyond those that describe conventional medicines currently in use. The author go on to state that while it is conceivable that each paradigm may be incorporated into the gene transfer system such has not been realized as of the publication of the textbook to tailor the gene transfer requirements of any specific disease (Exhibit 3, page 82, col. 1, lines 9-10). The authors also state that gene therapy is at its infancy and that gene transfer methodology is a limitation of the procedure (Exhibit 3, page 99, col. 2, parag. 1). In addressing HSV-1 as a vector for gene therapy, the authors state that this type of vector may be useful for treating intracranial tumors (Exhibit 3, page 89, col. 2, lines 1-3). Thus the author of the textbook chapter did not indicate that HSV-1, the specific example of appellant's

specification is routinely successful in gene therapy applications. The tone of the section on HSV-1 lends one to believe that HSV-1 vectors for successful gene therapy are yet to be designed. Thus these citations refute appellants allegations that gene therapy is another route of drug delivery for the artisan. The artisan does not indicate that such delivery is predictable. Further, the examiner has not ignored or dismissed the working examples. The rejection clearly states that which is lacking from the examples for enabling gene therapy.

Appellant argues that other routes of delivery and other neurotropic viruses need not be shown to be operational as working examples of every embodiment are not needed for enablement, and cites MPEP 2164.02 in support. Applicant argues that the specification discloses other routes of delivery and other neurotropic viruses that can be used in the claimed invention. Appellant argues that declarant Plunkett states that corneal abrasion would enable other peripheral routes of administration. Appellant argues that the examiner has not provided any reasonable basis for the enablement rejection.

Given the discussion above, it is apparent that appellant's specific example of HSV-1 and the HSV-1 latency promoter would not have been accepted by the artisan as enabling for gene therapy at the time of filing. Thus other neurotropic viruses would need to be described and taught as gene therapy delivery methods. The mere teaching of other neurotropic viruses and other routes of delivery is not sufficient given the unpredictable nature of gene therapy and the recognition by the art of that unpredictability. MPEP 2164.02 indeed states that working examples are not required, and none have been required. However, MPEP 2164.02 states that the specification must be enabling. Any

comments in this answer directed to working examples is not a statement that such are required for enablement, but an analysis as to why the examples do not provide enablement of the claimed invention. As the working examples are part of the specification, they are subject to analysis for supporting patentability. The instant analysis is based on the "Wands' Factors", and the "Wands' Factors" include an analysis of working examples.

B. Obviousness Rejection

In summary, claims 1- 9 are rejected under 35 U.S.C. § 103 as being unpatentable over Dobson et al (1989) J. Virol. 63, 3844-3851 in view of Nishimura et al (1986) Proced. Natl. Acad. Sci. 83, 7292-7296 . Dobson teaches the delivery of the rabbit ß-globin gene to the peripheral nervous system (PNS) of mice where expression of the ß-globin gene is regulated by the HSV-1 latency promoter (page 3850, col. 1, parag. 4, lines 1-6, page 3847, figure 5). Dobson does not teach the delivery to the CNS or the delivery of β-glucuronidase operatively or tyrosine hydroxylase linked to a promoter. However, Nishimura teaches the DNA sequence for β-glucuronidase (page 7294, figure 3). Motivation is offered by Dobson in stating that HSV-1 is an vector for the transfer of genes to neurons (page 3850, col. 2, parag. 3, lines 1-2). Further motivation is found in Dobson's teachings that HSV can produce latent infections in both the PNS and the CNS, and that the latency activated promoter, the LAT promoter, is active in such infections (page 3844, col. 1, parag. 1, lines 1-7). Thus given the teachings of Dobson that an HSV-1 vector delivers a gene of interest to the PNS and regulates expression of the gene from the LAT promoter, and that HSV inherently infects both the PNS and CNS, it would have

been obvious to the ordinary artisan had at the time of filing to deliver any gene of interest to the CNS by administering the vector of Dobson.

Appellant argues that Dobson teaches only peripheral nervous system infection with herpes virus, and expression of β-globin in peripheral neurons. Appellant's argue that examples 4 and 5 demonstrate CNS infection and successful gene expression in a mammal. Appellant argues that HSV-1 is a vector for transfer of gene to neurons of the PNS. Appellant argues that "neurons" imply within the CNS, but applies to both the CNS and the PNS. Appellant argues that CNS neurons are protected from exposure to foreign compounds, such as viruses, by the blood brain barrier. Thus appellant argues that gene delivery such as by Dobson to the PNS does not suggest to one of skill in the art that a similar vector could be used to deliver a gene to the CNS. Appellant argues that Nishimura in teaching only the DNA sequence for β-glucuronidase does not correct the deficiencies of Dobson. Declarant Plunkett supports these arguments regarding the blood brain barrier, and further states that the evidence presented in Dobson would not convince the artisan that one could infect the CNS with the same vector.

Appellant's assertions are not persuasive as Dobson clearly states that HSV-1 infection both the PNS and the CNS and establishes latency in both parts of the nervous system. While examples 4 and 5 demonstrate delivery of a DNA sequence encoding β-glucuronidase and it expression administering an HSV-1 vector comprising the DNA sequence operably linked to the LAT-1 promoter, such would have been obvious given the teachings of Dobson in view of Nishimura. As the art clear taught at the time of filing that HSV-1 can infect both the PNS and the CNS, the blood brain barrier is not a protector

against HSV-1 infection. The fact that the art teaches the infection of the CNS by HSV-1 indicates that the virus can overcome any protection afforded by the CNS by the blood brain barrier. Further, as pointed out by appellant and declarant Plunkett, neurons are contained in both the CNS and PNS. The vector of Dobson is described as faithfully expressing a foreign gene product stably in neurons in vivo , without any designation of where the neurons are located (page 3850, col. 2, parag. 3, lines 2-4). Thus, this statement and the knowledge that HSV-1 can infect both neurons of the CNS and the PNS, the artisan would be motived to administer the vector of Dobson and have a reasonable expectation of success in delivering a gene of interest to the CNS, and also expressing the gene in the CNS.

(14) Period of Response to New Ground of Rejection

In view of the new ground of rejection, appellant is given a period of TWO MONTHS from the mailing date of this examiner's answer within which to file a reply to such new ground of rejection. The reply may include any amendment or material appropriate to the new ground of rejection. Prosecution otherwise remains closed. Failure to respond to the new ground of rejection will result in dismissal of the appeal of the claims so rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Dr. D. Crouch
July 17, 1997

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